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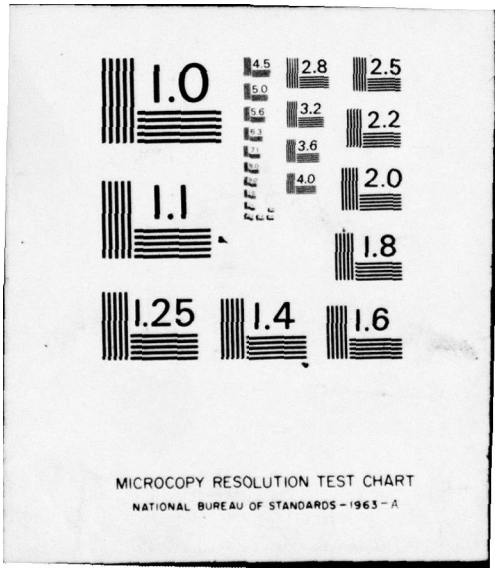
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Infectious illnesses of all varieties are accompanied by a complex group of metabolic, biochemical, endocrine, and physiological responses which, in turn, give rise to important nutritional consequences. The nutritional costs of an infection are greatest in the areas of protein and energy needs, but also involve the minerals, trace elements, and vitamins.

The cumulative depletion of body nutrients during an acute infectious process becomes maximal in the early phase of convalescence. The rate of nutrient depletion will slow down if an infection enters a subacute or chronic

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phase but, because cumulative deficits continue to increase, a state of dangerous cachexia may emerge. Infections are more severe if they occur in an already malnourished patient.

Nutritional supportive therapy should be employed to prevent or minimize the depletion of body stores during an infection, and to replace lost nutrients as expeditiously as possible during convalescence.

INFECTIOUS DISEASES: EFFECTS ON FOOD INTAKE AND NUTRIENT REQUIREMENTS

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William R. Beisel

TABLE OF CONTENTS

I. INTRODUCTION

All varieties of systemic infectious illnesses, whether acute or chronic, give rise to a complex array of metabolic, biochemical and hormonal responses within the host. These responses, in turn, initiate a number of nutritional consequences which vary in their magnitude and importance in rough proportion to the overall severity and duration of the illness.

It is thus not surprising that patients or laboratory animals with specific or generalized forms of nutritional deficiency are frequently unable to resist, in a normal manner, a disease due to microbial organisms (Scrimshaw et al., 1959). Nonspecific host defensive mechanisms as well as specific forms of immune responsiveness are impaired in patients with severe protein-energy malnutrition (Suskind, 1976). Nutritionally induced impairment of host resistance is seen most commonly in the infants and children of the underdeveloped nations where various forms of protein-energy malnutrition are commonplace. An impaired nutritional status also contributes to defective host resistance in another important group of patients, i.e., hospitalized individuals who have failed to maintain (or to receive) an adequate dietary intake as a result of their disease process, or as an iatrogenic consequence of one or more commonly utilized forms of cytotoxic therapy now employed in advanced medical center (Bistrian et al., 1975).

Acute and chronic infections deplete the body of important stores of nutrients, and the resultant nutritional deficits can then render a patient more susceptible to secondary or superimposed infections. Such a sequence has variously been described as a vicious circle or a downhill spiral. Measles, pertussis, and the common respiratory and diarrheal diseases of children are the most important infections in terms of their propensity to initiate such a lethal sequence (Mata et al., 1977). Thus, it can be argued

that a closely spaced series of common childhood infections is per se the most important single factor in causing long-term malnutrition, growth retardation, and high infant mortality rates in underdeveloped nations (Mata et al., 1977; Whitehead, 1977).

Much new information has been uncovered in recent years to document the extent and complexity of the nutritional responses that occur in patients who develop infectious diseases or microbial toxemias. It is now possible to list several thousand different kinds of biochemical, nutritional, metabolic and hormonal responses to infection (Beisel, 1976). Some responses are relatively unique and are seen only in certain kinds of infection. In contrast, many other metabolic and endocrine responses occur in a common, virtually stereotyped pattern whenever an infectious process is accompanied by fever.

Despite the magnitude and complexity of these host responses, many of them can now be explained through an improved understanding of the basic molecular mechanisms which cause them to occur. Thus, current knowledge about fundamental cellular mechanisms now makes it possible to identify and comprehend some of the major forms of host nutritional response which typify an acute infectious illness, no matter what its causative microorganism.

II. NUTRITIONAL RESPONSES TO ACUTE FEBRILE INFECTIONS

A. The Catabolic Response

The catabolic response of an infected host is of major nutritional importance, as evidenced by the clinical signs of wasting seen in many patients, as well as the increased incidence of long-term serious complications following the original illness. An acute infectious process severe enough to induce fever is generally accompanied by an acceleration of catabolic processes. The catabolic phenomena are similar in many respects to those seen after elective surgery, trauma, or burns. The magnitude of catabolic

response can generally be equated with the severity of cellular damage or tissue injury, with extensive burns being the primary example of the most extreme form of hypercatabolic stress. All of these kinds of massive cellular damage initiate secondary catabolic responses which result in accelerated consumption of stored body nutrients, depletion of muscle mass, and absolute losses of body constituents. The latter can be measured, in part, by metabolic balance techniques. Skeletal muscle is the site of the most prominent catabolic changes during even mild, short-term infections. Enzyme activity is diminished in muscle, creatine phosphokinase escapes into the serum, the histological ultrastructure develops focal changes, electromyographic abnormalities can be detected, and maximal isometric muscle strength becomes decreased (Friman, 1976).

B. Patterns of Catabolic Loss of Nutrients

The catabolic responses to infection are not initiated when invading microorganisms first penetrate into host tissues, nor do they begin during the incubation period of an infection. Rather, the catabolic responses generally become evident only after fever has developed. On the basis of prospective studies conducted during experimentally induced infections in well-nourished subjects (Beisel et al., 1967), it has been possible to demonstrate that negative body balances for most elements typically begin shortly after the onset of fever. Negative body balances of nitrogen occur during a large variety of febrile infections caused by many different types of microorganisms. The negative balances of body nitrogen continue throughout the course of most short-term febrile infections in previously healthy persons and are generally reversed within a day or two after the cessation of the fever. Although the body can then begin to retain nitrogen and other elements, in order to reconstitute the cumulative losses suffered during an illness, the

full recovery period may require several weeks after even a brief, relatively mild infection.

Losses of other key intracellular elements, such as potassium, magnesium, phosphate, sulphate, and probably zinc, all appear to occur with a pattern and magnitude proportional to the losses of body nitrogen. A number of separate factors have been recognized which contribute to these absolute, measurable losses of body constitutents.

C. Altered Gastrointestinal Function

In most illnesses, a combination of anorexia and nausea, possibly of central nervous system origin, causes the patient to stop eating solid foods. In infections where vomiting or diarrhea are important components of the illness, body fluids and nutrients can be lost directly and in sizable quantities from the gut. Anorexia, along with nausea and sometimes vomiting, tends to be present consistently during most acute infections and is a major contributing factor to negative body balances. Depending upon its severity, anorexia will reduce the intake of dietary nutrients to varying degrees. Unless anorexia-induced semistarvation is reversed by attempts at forced or gavage feedings or by the administration of intravenous nutrients, the presence of anorexia contributes to negative body balance by diminishing the consumption of dietary nutrients throughout the acute stages of an infection. We do not yet know the exact pathophysiologic mechanism by which an infection is able to initiate anorexia. Although anorexia is an important problem, a diminished intake of food accounts only partially for the severity of negative body balances. This is because starvation <u>per se</u> does not normally accelerate the catabolism of labile body proteins.

Thus, the metabolic responses of an infected patient do not resemble those of an otherwise healthy person who is placed on a starvation regime

(Wannemacher, 1977). During simple starvation, metabolic processes adjust rapidly to conserve both protein and amino acid nitrogen. The body does this by becoming increasingly dependent upon its lipid sources of fuel, especially through the hepatic production of ketone bodies from fatty acids. The stores of depot fat are also used as the source for most of the metabolizable energy needed to allow cellular functions to continue. In contrast, during acute infections, the body seems unable to conserve its supplies of amino acids and many of them are shunted into gluconeogenic pathways. Also, as has recently been shown (Neufeld et al., 1976; Blackburn, 1977), the body seems unable to initiate or sustain the production of ketone bodies within the liver during acute infections.

The differences between simple starvation and the illness-induced starvation of infection are of major practical importance from a nutritional point of view, inasmuch as the daily catabolism of body nitrogenous constituents continues unabated or becomes accelerated in the infected subject despite a concomitant reduction in the intake of dietary sources of protein and energy.

In addition to causing anorexia and disturbances of gut motility, pathogenic intestinal microorganisms can cause destructive and inflammatory lesions within the mucosa, intestinal wall, and lymphatic system which can interfere with absorptive functions (Rosenberg et al., 1977). Intestinal parasites can also damage the intestinal mucosa and lead to a direct loss of blood cells and protein. Parasites may become sufficiently massive in size or number that they can compete with the absorptive mechanisms of mucosal cells for key nutrients contained within intestinal luminal fluids. Changes in the number, composition, and location of intestinal microflora resulting from antibiotics or purgative therapy can also interfere with digestive

functions. The enterotoxins appear to alter the transport mechanism across intestinal mucosal cells, to alter intestinal motility, and indirectly to alter rates of blood flow through the abdominal viscera. A generalized infectious process or endotoxemia can produce similar effects on intestinal function, even in the absence of any localization of infection within the gut. Intestinal functions may also be altered because of changes in the turnover and maturation rates of intestinal mucosal cells. Thus, an impaired absorption of nutrients may be due to either the direct or indirect gastrointestinal effects of an infectious process.

D. The Role of Fever

A second major factor which contributes to the hypercatabolic aspects of infection is the presence of fever. This physiological response has long been known to increase the rates of basal body metabolism. Estimates of the magnitude of increase range from 10 to 15% of basal for each °C increase in core temperature (Keusch, 1977). Metabolic balance studies performed in healthy, noninfected adult volunteers show that losses of body nitrogen and other key intracellular elements occur when fever is initiated artifically by physical manipulation of the environmental temperature and humidity. The metabolic responses to artifically induced fever resemble quite closely the patterns of loss that accompany an infection-induced fever. Thus, fever per se can account for many of the losses of body nutrients measured during an acute infectious illness.

Other factors are known to contribute to direct losses of body nutrients. Direct intestinal losses accompany the occurrence of diarrhea or vomiting, and dermal losses are magnified if diaphoresis is a prominent symptom. Some nutritional changes can be ascribed directly to the presence of invading microorganisms in the tissues of the host. Organism-induced changes are more

difficult to quantify in an in vivo study than the deficits which can be ascribed directly to fever or to an impaired dietary intake. They are dependent upon the need or replicating microorganisms to acquire important key nutrients such as the amino acids, minerals, vitamins, and other co-factors. Such an organism-induced diversion of host nutrients has been shown best with relatively large size invaders, such as the parasites, which utilize measurable quantities of host-derived vitamins and amino acids for their growth.

E. Clinical Assessment of Catabolic Losses

Available biochemical and histological evidence would suggest that the nitrogen which is lost from the body is derived primarily from protein sources within skeletal muscle and skin (Friman, 1976; Wannemacher, 1977). Thus, the wasting systemic effects of an acute infection can be quantitated fairly well through the use of simple clinical measures. Daily determinations of body weight serve as a highly useful guide, although retention of excess body water may obscure for a time the extent of losses in cell mass. Measurements of upper arm circumference and skin-fold thickness can be used to estimate muscle mass and subcutaneous fat (Bistrian et al., 1975). Relatively simple laboratory tests can also be used to help determine the severity of the catabolic response during the acute phase of illness. Twenty-four hour urine collections can be measured for their content of total nitrogen and creatinine. A healthy adult adapted to brief fasting will lose only 5 gm/day of nitrogen; moderately severe wasting illnesses cause losses of 10 to 15 gm/day while severely catabolic patients will lose in excess of 20 gm/day. A more precise measurement for determining degradative losses of skeletal muscle contractile protein can be achieved by daily assay of 3-methylhistidine losses in urine at laboratories prepared to run this test

(Wannemacher et al., 1975; Long et al., 1977). The cumulative effects of a catabolic illness on visceral protein adequacy can be estimated indirectly by declining serum concentrations of albumin and transferrin.

F. The Anabolic Response to Acute Infection

Every functional host defensive mechanism employed to prevent or overcome a microbial infection is dependent in some basic molecular aspect upon the ability of body cells to synthesize protein. Thus, heightened anabolic cellular activity and additional molecular capabilities for protein synthesis are required to contribute to survival capabilities. Proteins of many varieties are necessary for the creation of new body cells such as lymphocytes, macrophages, and neutrophils, and for the formation of their specialized organelles; structural proteins are required for the repair of damaged tissues; additional intracellular enzymes must be synthesized in many existing cells to allow appropriate changes in molecular mechanisms to occur during the secondary metabolic responses to the infectious process; and a wide assortment of individual proteins must be synthesized for secretion into circulating body fluids. These latter species include all of the immunoglobulins and acute-phase reactant glycoproteins, certain protein hormones, the various components of the complement and coagulation cascade systems, as well as other diverse circulating proteins such as interferon.

The magnitude and clinical prominence of the catabolic response to acute infection, obscured for many years, the fact that accelerated protein anabolic activity was present concomitantly. Metabolic balance techniques are only able to indicate the total amounts of a measurable element that are retained or lost by the body; balance techniques do not provide any information concerning the manner in which the internal body metabolism may be altered with respect to the element under study. Thus, in addition to the overt,

measurable losses of many body constituent elements during an infection, there are also important concomitant changes of a functional nature in the priorities by which body cells utilize their available substrates to manufacture key products (Powanda, 1977). These functional changes seem to occur as purposeful physiological responses by the body, and they are often manifested by the redistribution of essential nutrients within body pools, or by the reordering of priorities which regulate the entry of nutrient substrates into certain metabolic pathways. As examples, amino acids are shunted into the liver and utilized for the accelerated synthesis of acute-phase reactant proteins and for gluconeogenesis. On the other hand, a markedly increased amount of tryptophan is shunted into the kynurenine pathway of hepatic cells during various kinds of infection, especially typhoid fever. Although the purpose of this shunting is not clear, it results in an exaggerated excretion of diazo reactants via the urine (Rapoport and Beisel, 1971).

G. The Key Central Role of the Liver in Metabolic Responses to Acute Infection

Much recent evidence has been derived to show the importance of the liver in contributing to a redirection of metabolic body functions as a secondary response to infectious disease stress. Several forms of hepatocyte response have been identified (Powanda, 1977; Wannemacher, 1977) in addition to alterations in tryptophan metabolism already described. These responses involve the accelerated uptake of amino acids and the trace metals zinc and iron from serum, and a reorientation of the protein manufacturing processes with the hepatocytes to emphasize an accelerated synthesis and release of many different acute-phase reactant glycoproteins; these include haptoglobin, $alpha_1$-antitrypsin, $alpha_1$-acid glycoprotein (orosomucoid), C-reactive protein, fibrinogen, the third complement of complement, and ceruloplasmin.

At the same time, the liver is also being subjected to multiple hormonal influences which result in major changes in carbohydrate homeostasis. The interacting hormonal effects combine to initiate the breakdown of hepatic glycogen stores into glucose and the accelerated synthesis of new glucose within the hepatocytes (Long, 1977). Substrates for accelerated gluconeogenesis include lactate, pyruvate and certain amino acids, especially alanine and glycine, which are released in greater-than-normal quantities from skeletal muscle subsequent to the catabolic changes in the contractile proteins, actin and myosin.

The molecular mechanisms of the liver which regulate both the metabolic degradation and the synthesis of various lipids are altered during infection, as is the hepatic release of transport lipoproteins.

Despite the complexity of the widespread infection-induced changes in amino acid and protein metabolism, Wannemacher (1977) found it possible to estimate the rates of changes in protein metabolism of key body organs and tissues and to contrast them with changes that would result solely because of starvation. As shown in Figure 1, an adult who is adapted to simple starvation will lose approximately 4 gm of nitrogen in the urine each day. This nitrogen is derived from the catabolism of about 25 gm of body protein; approximately 20 gm of this total are estimated to come from the skeletal muscle. Because fat depots can provide much of the needed metabolizable energy during simple starvation, through the conversion of fatty acids into ketones which serve as direct forms of cellular fuel, the body is largely able to spare its pools of labile protein and to maintain its ability for many days to synthesize its vital visceral and leukocytic proteins. Thus, the approximate equivalent of amino acids derived from only 15 gm of body protein need to be diverted each day for the purpose of producing glucose within the liver and kidneys.

In contrast, during an acute infection, the body does not cut back on its excretion of nitrogen via the urine, and large amounts of protein contained in skeletal muscle and skin are degraded. There is an accelerated turnover of leukocytic proteins and an accelerated synthesis of acute-phase reactant globulins within the liver. The contractile proteins of skeletal muscle serve as the major pool of relatively labile protein which can be used rapidly as a source of amino acids to meet these needs, as well as to provide metabolizable energy during acute febrile infections. Importantly, in a moderately catabolic illness, approximately 75 gm of skeletal muscle protein must be degraded each day to supply amino acids as a primary substrate for glucose synthesis within the liver.

H. Carbohydrate Metabolism

Infection-induced alterations in carbohydrate metabolism have important nutritional consequences because of changes in substrate requirements. The initial host responses involve an accelerated consumption of glucose by peripheral body cells, and an accelerated production and release of glucose by the liver. These changes are brought about, in large measure, by multiple hormonal changes which include increased concentrations in plasma of glucagon, growth hormone, adrenal glucocorticoids, catecholamines, and insulin (Ryan et al., 1974; Long, 1977). Accelerated gluconeogenesis leads to modest hyperglycemia despite the elevation of plasma insulin values. Although this paradox is in keeping with clinical evidence of transient insulin resistance in diabetic patients who develop an infection, the anti-lipolytic effects of infection have been ascribed, in part, to elevated insulin values (O'Donnell et al., 1976).

Deficits in peripheral fuel supplies with respect to glucose and fat are made up through the use of gluconeogenic amino acids as substrates, which

are derived, in turn, through accelerated proteolysis, oxidation of the branched-chain amino acids within muscle, and subsequent increase in the production and release of alanine from muscle (O'Donnell et al., 1976).

When sepsis becomes overwhelming in severity, peripheral fuel requirements cannot be met (Wilmore, 1977). Blood and tissue carbohydrate supplies become exhausted, metabolic rates fall precipitously, and body temperatures plummet as terminal events. Such agonal findings in experimental animals could be due to an exhaustion of substrate pools, to a failure of hepatic enzymatic mechanisms for maintaining gluconeogenesis, or to a combination of both defects. Analogous events in man include the hypoglycemia of neonatal sepsis (Yeung, 1970) as an example of substrate exhaustion, and the hypoglycemia of severe hepatitis (Felig et al., 1970) as an example of hepatic enzyme dysfunction.

I. Lipid Metabolism

It is not clear why an infected host is unable to utilize rapidly the energy potentially available in fat depot stores, but the capacity for ketone body synthesis appears to be lost during acute febrile illnesses (Neufeld et al., 1976). As shown in animals, the liver takes up fatty acids from plasma at an accelerated rate and accelerates its synthesis of both triglycerides and cholesterol during acute infections (Fiser et al., 1972). In gram-negative infections of man, peripheral tissues seem unable to remove triglycerides from the plasma with sufficient rapidity to prevent their marked accumulation and the occurrence of hypertriglyceridemia and hyperlipemia. In most severe infections, the liver also shows histological evidence of an intracellular accumulation of lipid droplets (Blackburn, 1977).

J. Vitamin Metabolism

The altered rates of cellular metabolism during acute infections may also involve the vitamins, although this field of knowledge has largely been neglected (Beisel, 1976). Available information does indicate that there is accelerated utilization or redistribution of most vitamins during the course of an infection, and that severe infections can occasionally precipitate the overt clinical signs of deficiencies in single vitamins (Scrimshaw et al., 1959).

K. Electrolyte Nutrition in Acute Infection

Electrolyte homeostasis can become dangerously disturbed during different kinds of infection and produce life-threatening problems at each end of the dehydration -vs- overhydration axis (Beisel, 1976). Emergency therapeutic measures involving salt and water nutrition are required when these derangements are recognized.

On the one hand, fulminant massive diarrhea can lead to direct iso-osmotic losses of water and electrolytes sufficient to produce extreme dehydration, vascular collapse, and terminal circulatory failure. Loss of bicarbonate ions in diarrheic stools can produce metabolic acidosis. In contrast, a loss of potassium ions associated with chronic, low-volume diarrhea can produce cumulative nutritional deficits of potassium sufficient eventually to cause metabolic alkalosis and hypokalemic nephropathy (Beisel, 1976).

At the other end of the spectrum, an exaggerated secretion of aldosterone occurs during generalized infectious illnesses. This causes kidneys to retain both sodium and chloride, and secondarily, to retain excess body water. Some degree of dilutional overhydration is present in most severe infections, but it is not usually life-threatening.

An inappropriate secretion of antidiuretic hormone may occur as an additional superimposed problem in some severe infections, especially those with central nervous system localization (Feigin and Kaplan, 1977). An impaired integrity of cellular membrane function in infections such as Rocky Mountain spotted fever may also cause sodium to accumulate within cells. With either of these latter complications, dilutional hyponatremia becomes a dangerous problem which can produce fluid overload of the cardiovascular system, with generalized as well as pulmonary edema. Treatment of these latter conditions requires a careful and judicious witholding of salt and water along with, in some instances, emergency measures to support cardiopulmonary functions.

III. NUTRITIONAL ASPECTS OF CHRONIC INFECTION

The multifaceted nutritional consequences of an acute infection in a previously healthy person can now be evaluated with considerable insight. In contrast, far less is known about the nutritional responses which may accompany the transition of an acute illness to a subacute or chronic one, or about the quantitative or qualitative nature of nutritional responses which develop when an infection occurs in an already malnourished person.

When an infectious process continues into a subacute or chronic stage, the amount of nitrogen lost from the body tends to diminish progressively each day. Eventually a new state of near-equilibrium becomes established at a cachectic level, with marked depletion of both the labile protein and depot fat stores of the body. Recent prospective studies also show that mild infections may fail to initiate the anticipated loss of body nitrogen if they occur in obese patients who previously had become adapted to either fasting or a protein-sparing, semifasting type of diet (Bistrian et al., 1977).

A febrile infection that develops in a patient already suffering from severe protein-energy malnutrition is accompanied by an increased consumption of oxygen, but malnourished patients may respond with relatively small absolute losses of body nitrogen. Despite evidence for some conservation of nitrogen, the total loss of body mass may be substantially greater on a percentage basis than the losses seen when a well nourished person develops an infection (Mata et al., 1977). The fact that smaller absolute amounts of nitrogen are lost (after the labile protein pool has virtually become exhausted) does not mean that the chronically infected or malnourished host is enjoying a new, favorable state of metabolism. Rather, this evidence of depleted labile protein stores is a danger sign with potentially grave implications. A given infection runs a far more severe course and has a far higher mortality rate when it occurs in a malnourished person (Mata et al., 1977).

Thus, in protein-depleted patients, measurable catabolic losses of body nitrogen are not linked directly to the presence of fever or the infectious process. In contrast, certain of the anabolic phenomena involving protein formation, i.e., the accelerated synthesis of acute-phase serum glycoproteins, are known to occur during infection or inflammation even in the presence of a severe, symptomatic depletion of body protein and energy stores (Patwardhan et al., 1971; Cockerell, 1973).

IV. NUTRIENT REQUIREMENTS DURING INFECTION

Despite the fact that acute infections cause measurable losses of many nutrients from the body and are accompanied by accelerated expenditures of body energy stores, finite guidelines for minimal daily requirements of protein, energy, and vitamins have not been widely utilized or accepted during periods of acute infectious illness. Not only are minimal requirements

hard to quantify during an acute infection, but some theoretical doubts can be raised concerning the need to replace (or maintain) body nutrient stores lost during the course of an acute illness. This unsettled situation creates a continuing dilemma for the nutritional planners as well as for medical practitioners.

If the measured, absolute losses of body nutrient stores during infection and the physiological redistribution of nutrient stores within the body are both regarded as wasteful processes (since they ultimately produce a clinical wasting of body tissues), then it would seem therapeutically desirable to prevent these losses during the course of an illness or to correct them as soon as possible during convalescence. On the other hand, fever has been regarded in some of its aspects as a purposeful device to eliminate microbial invaders and anorexia appears to be a "natural" host response because it occurs so consistently during infection. Other metabolic and physiological responses which reset the metabolic priorities for the production of glucose and proteins may also have positive benefit. If these responses are in fact purposeful defensive mechanisms, it can be argued that vigorous attempts to counteract or reverse them may not necessarily be helpful for the host. Alternatively, therapeutic attempts to supply substrate nutrients being used for these metabolic purposes would be in conflict with the concept that anorexia may have a useful purpose.

A. Beneficial Aspects of Host Nutritional Responses

The problem as to whether or not fever is beneficial for the defense against microbial organisms has long been debated. Hyperpyrexia is known to help eliminate at least two disease-producing microorganisms, Neisseria gonorrhoeae and Treponema pallidum. On this basis, induced fever was employed as therapy in earlier years to treat infections due to these organisms. It

has recently been shown that both cold- and warm-blooded animals, e.g., lizards (Kluger et al., 1976) and young rabbits (Satinoff et al., 1976), will move spontaneously into a high temperature area of their cages if they are injected with bacterial lipopolysaccharide endotoxin. Such an innate behavioral response causes the body temperature of these animals to increase by several degrees and supports the view that fever is beneficial (Keusch, 1977).

Powanda (1977) has recently summarized evidence suggesting that many of the metabolic changes observed during an infectious or inflammatory disease are, in fact, component aspects of a purposeful redistribution of amino acids from peripheral tissues to the liver for various aspects of host defense including the synthesis of acute-phase glycoproteins. When body cells engage in phagocytic activity, they liberate endogenous mediating substances into the plasma which, in turn, trigger the initiation of fever, neutrophil release from the bone marrow, glucagon release from the pancreas, accelerated uptake of amino acids, zinc and iron by the liver, and accelerated synthesis of acute-phase glycoprotein within the liver. Thus, phagocytosis is theorized to be the initiating stimulus for these many early host defensive responses which occur prior to the development of specific immunity.

Powanda (1977) postulates that each of the individual acute-phase reactant proteins produced by the liver during acute infectious or inflammatory states has some purposeful role to play in host defense. The functional role of this diverse group of proteins has not been clearly defined. However, alpha$_1$-acid glycoprotein, also known as orosomucoid, appears to interact with platelets to aid in their binding to collagen, as well as to stimulate the formation of collagen fibers. These properties

may have value in the healing of infection-induced lesions within tissues. Alpha$_1$-antitrypsin is capable of inhibiting the action of a large variety of proteinases, and may thus function to limit the possible damage to tissues surrounding the site of a localized infectious process. Since alpha$_1$-antitrypsin can also inhibit plasmin and Hageman factor cofactor, it might also tend to inhibit disseminated intravascular coagulation. Haptoglobin acts rapidly to form complexes with free hemoglobin in plasma; the complexed hemoglobin can then be removed from the circulation by reticuloendothelial cells. This action of haptoglobin appears to be especially important in infections such as malaria which have an important hemolytic component. In addition, haptoglobin has an associated glucosamine saccharide which could reduce damage due to the release of cathepsin B from phagocytes or other injured cells. Ceruloplasmin serves as a copper transport protein and appears to assist in the normal movement of iron from cells to plasma through its ferroxidase activity. Ceruloplasmin may also be capable of oxidizing catecholamine and serotonin. C-reactive protein has recently been shown by Croft et al., (1976) to bind selectively to thymus-derived lymphocytes when lymphoblastic transformation is stimulated by antigens, suggesting that this acute-phase reactant may also play a role in the regulation of host immunological responses.

In contrast to the apparently purposeful increase in the synthesis of acute-phase reactant serum proteins, albumin concentrations tend to decline appreciably during most severe infections. It is not clear whether the decrease in plasma concentration of albumin results from a decreased rate of synthesis, an increased rate of degradation, an alteration in distribution space, or from some combination of these possibilities. If albumin functions in part as a circulating pool of labile protein, then an infection-induced

decline in albumin concentration may serve to make additional amino acids available for the production of more critically needed body proteins.

The propensity of the host to synthesize acute-phase reactant glycoproteins during acute infection seems to represent a primitive form of host defense, since studies both in man and experimental animals show that the body will still synthesize large quantities of these glycoproteins in children with kwashiorkor or marasmus (Patwardhan et al., 1971) or in animals that have been experimentally infected after a prolonged period of starvation (Cockerell, 1973). These observations suggest that the body is willing to sacrifice its somatic proteins in order to preserve its capability for synthesizing visceral proteins during an infection.

The sudden increase in the uptake of iron and zinc by the liver during an infectious process serves to depress their respective concentrations in plasma without any appreciable or concomitant decline in the plasma concentration of their carrier products. Responses involving these trace elements may also have a beneficial role in host defense. Weinberg (1974) has argued that the decrease in serum iron concentration (with a concomitant increase in the amount of unbound transferrin) serves as an important mechanism for preventing an invading microorganism from obtaining the iron it required to allow it to proliferate. Because of its high affinity constant for iron, the unbound transferrin is able to compete successfully with bacteria-produced siderophores, and thereby block the uptake of the microorganisms. Clarkson and Brohn (1976) recently utilized this concept in an attempt to devise a nutritional form of chemotherapy which could eliminate the parasite Trypanasoma brucei brucei from the blood of rats and mice. An iron chelator, salicyl hydroxamic acid, and glycerol were administered concomitantly in an attempt to block both aerobic and anaerobic

glucose catabolism of the parasites. This therapy led to a prompt and dramatic disappearance of parasites from peripheral blood for a period of one week. Although this approach to therapy was not curative, it was of considerable theoretical importance, because it demonstrated that an understanding of the basic molecular mechanisms involved in host-microorganism interactions could be used to favor the host and suppress the invader.

Zinc is required for the activation of hepatic RNA synthetases and for the synthesis of protein by hepatic ribosomes. Since zinc has also been shown to inhibit phagocytosis, its accelerated flux into the liver could conceivably permit more active phagocytic activity in peripheral tissues (Chvapil, 1976).

B. Depletion of Host Nutrient Stores

The preceeding types of data support the concept that fever and many of the nonspecific metabolic responses to infection do contribute to host survival, and thus their costs, in terms of depleted pools of body nutrients, should not be considered as wasteful expenditures. Regardless of whether these nutritional costs are purposeful or wasteful, they can be sizable. Although the normally nourished person can afford, for a time, to pay the nutritional costs of a brief infectious illness, a continuing severe depletion of essential nutrients will ultimately diminish the changes for survival.

The interrelated variables of severity and duration of an illness must therefore be considered in assessing the probable ultimate magnitude of accumulated nutritional costs. These costs can be reduced by bringing the infectious microorganism under control as rapidly as possible, by preventing excessive hyperthermia, and by minimizing nutritional losses during the illness. If the body is purposefully redistributing its stores of key nutrients and reordering its priorities for nutrient utilization, it would

seem theoretically sound to provide key nutrients as a form of supportive therapy during the illness. Many decades of clinical experience support this approach with respect to the needs for an added intake of protein and energy sources during a severe infection, especially one that is not susceptible to any available antimicrobial therapy.

C. Replacement of Host Nutrient Stores

There is general agreement that depleted nutrient stores should be reconstituted as soon as possible during convalescence after fever and anorexia have ceased. A healthy person generally experiences and promptly recovers from a large number of separate acute infections during his lifetime. Thus, the depletion of body nutrients which occurs during an acute or chronic infection is not necessarily a long-term threat to survival, for when the causitive microorganism is controlled, pools of body nutrients can be restored by appropriate dietary measures. Even a brief self-limited viral infection, however, has been shown to produce deficits in body nitrogen that take approximately three weeks to replace after the convalescent patient begins eating a full diet which previously maintained him in a normal state of nitrogen balance (Beisel et al., 1968). Prospective studies conducted during experimentally induced infections show that the cumulative losses of various body nutrients actually reach their largest values during the first few days of early convalescence. The early post-febrile period is the time that a patient recovering from an infectious illness is most susceptible to a secondary or superimposed microbial invader.

Generalized nutritional deprivation, whether occurring in children or adults, diminishes host resistance through a variety of mechanisms (Suskind, 1976). Although cell-mediated immunity seems to be most susceptible, severe protein-energy malnutrition can also cause derangements in humoral immunity

as well. The synthesis of specific secretory immunoglobulin appears to be impaired by malnutrition, as is the production of complement components and the ability of phagocytic cells to perform in a normal manner. Nonspecific host defensive mechanisms are adversely influenced by generalized malnutrition, and isolated deficiencies of single essential nutrients, such as vitamins, can also lead to impaired host resistance (Beisel, 1976, 1977).

Thus, prompt and expeditious measures to correct the nutritional depletion known to accompany acute infectious diseases should be an important goal in the management of convalescent patients. Achievement of this goal would have definitive rewards. In addition to shortening the convalescent phase of illness, the rapid restoration to normal of nutritionally impaired host defensive mechanisms would help to prevent recurrent or superimposed infections that lead to the downhill spiral or vicious cycle common in malnourished patients. Unfortunately patients and physicians alike generally assume that a complete cure has been achieved when the fever and symptoms of acute illness disappear. A prompt restoration of depleted body nutrient stores may thus be left to chance or the vagaries of dietary practices by individual convalescent patients.

D. Estimation of Nutrient Requirements

In a recent workshop reviewing the impact of infectious disease on nutritional status of the host (Beisel, 1977), it was possible to arrive at certain approximations concerning nutritional requirements during and immediately after an infection. Since protein losses during acute infection amount to approximately 0.6 to 1.2 g/kg/day in adults and since protein synthetic competence is the most important factor common to all host defensive mechanisms, extra protein feedings are required. For children suffering from acute infectious illness, 1.5 g/kg/day of protein will be

needed. Whether attempts should be made to give additional protein feedings during the period of acute fever and severe anorexia would depend, in large measure, upon a clinical evaluation of the nutritional status of the patient and the anticipated duration of illness. In any event, an increased protein intake should be utilized during convalescence to replace the calculated cumulative loss of body protein. Such convalescent period requirements for dietary protein involve increases of 0.3 to 0.5 g/kg/day above the recommended minimal normal protein requirements in adults until the cumulative deficit is corrected. Patient acceptance for this increase in dietary protein may be enhanced by virtue of a hyperphagocytic period which some observers have noted during convalescence from an acute infection.

An increase in caloric intake is also needed, based upon the accelerated expenditure of energy stores associated with fever and illness. These increases should optimally achieve a total caloric intake during a period of infection that is 10 to 30% higher than the minimal normal needs. The increase in caloric intake should be approximately 20 to 40 kcal/kg/day in adults, 100 to 150 kcal/kg/day for children and 200 kcal/kg/day for infants. This increase in caloric intake should be maintained throughout the convalescent period to assist in obtaining the full value from ingested dietary protein. The minimum recommended intake of vitamins should be maintained throughout a period of acute infectious illness.

The guidelines for increasing the dietary intake of protein and energy sources should also be followed in patients with a chronic long-term infectious process. In those patients who suffer a low-grade chronic infection without severe febrile episodes, it should be possible to replace or correct the depleted body nutrient stores at the same time that attempts are being made to bring the infectious process under control.

Optimal management for a patient with either an acute or chronic infection requires that nutritional considerations be included as one of the important aspects of general supportive therapy. A nutritional support plan should be individualized to include the anticipated needs during both the acute and convalescent phases of illness. In addition to considerations based upon the probable course of the disease process, an individualized nutritional assessment is needed to evaluate the degree of protein depletion and hypermetabolism of each patient. This is most important in severe or prolonged infections. Body weight should be measured sequentially as one of the most available and valuable of the clinical guides. Measurements of the total nitrogen, creatinine, and ketone body content of 24-hour urine collections are useful to help evaluate the magnitude of ongoing losses of body protein, and the presence, if any, of nitrogen-sparing conpensatory responses. Measurements of serum albumin and transferrin concentrations can help assess long-term visceral protein depletion, and measurements of oxygen consumption rates can be measured as a guide to the degree of hypermetabolism present in an individual patient.

V. SUMMARY

Infectious illnesses of all varieties are accompanied by a complex group of metabolic, biochemical, endocrine, and physiological responses which, in turn, give rise to important nutritional consequences. The nutritional costs of an infection are greatest in the areas of protein and energy needs, but also involve the minerals, trace elements, and vitamins.

The cumulative depletion of body nutrients during an acute infectious process becomes maximal in the early phase of convalescence. The rate of nutrient depletion will slow down if an infection enters a subacute or

chronic phase but, because cumulative deficits continue to increase, a state of dangerous cachexia may emerge. Infections are more severe if they occur in an already malnourished patient.

Nutritional supportive therapy should be employed to prevent or minimize the depletion of body stores during an infection, and to replace lost nutrients as expeditiously as possible during convalescence.

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Caption for Figure

FIG. 1. A comparison between "starvation-adapted" and fasting septic adult patients with respect to the estimated daily flux of amino acids (quantified in terms of protein) among body compartments. Note that in septic patients the catabolism of somatic proteins of muscle and skin persists at a high level and that amino acids are diverted in large quantities for the synthesis of glucose, acute-phase globulins, and leukocytic proteins (Wannemacher, 1977).

PROTEIN (g/DAY) METABOLISM